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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,053	12/20/2004	Heidi S. Philips	P1943R1	5432

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,053	PHILIPS ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/15/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of group 11, claims 43-81, SEQ ID NO:2, encoded by SEQ ID NO:1, and glioma, in the reply filed on 02/11/08 is acknowledged.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, group 11, claims 43-81, a method for killing glioma cells, using an antibody that binds to SEQ ID NO:2, are examined in the instant application.

The embodiment of claims 43-81, as drawn to a method for treating cancer, using an antibody to SEQ ID NO:4, or a method for treating cancer, which is a breast cancer cell, a colorectal cancer cell, a lung cancer cell, an ovarian cancer cell, a central nervous system cancer cell, a liver cancer cell, a bladder cancer cell, a pancreatic cancer cell, a cervical cancer cell, a melanoma cell, a leukemia cell, using an antibody to SEQ ID NO:2, has been withdrawn from consideration as being drawn to non-elected invention.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-81 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. The claims are evaluated for enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows: (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.The specification discloses the nucleic acid SEQ ID NO:1 (TAT4434 or DNA98566)(p.6) is overexpressed in gliomas as compared to normal brain tissue, using microarray (Example 3, on p.80-81). The specification discloses that an IgG (Hu4D5) with Fc mutation replacing amino acids T307, E308, and N434 with Alanine has a 12 fold increase in binding to frozen unfixed section of human glioblastoma as compared to wild type IgG1, at acidic pH 6.0 (Example 11 on pages 88-89). The specification discloses that binding of the mutant IgG to the neonatal Fc receptor (FcRn) expressed on gliomas is pH dependent, i.e. binding at acidic pH but not at neutral pH 7.4 (p.88, paragraph before last).

The specification however does not have any data or objective evidence that gliomas could be successfully killed or treated using an antibody to SEQ ID NO:2, including its Fc variant.

1. Claims 43-81 are rejected under 112, first paragraph, for lack of enablement for **a method for treating glioma, using an antibody to SEQ ID NO:2.**

One cannot predict that gliomas would be successfully treated using an antibody to SEQ ID NO:2, including its Fc variant, in view that immunotherapy of cancers is highly unpredictable, especially for brain cancer, which has an additional problem with blood brain barrier. Roopenian et al, Nature Reviews, Immunology, 2007, 7: 715-723, teach that unlike the endothelium in other organs, the cerebral vascular endothelial cells are joined by tight junctions that prevent the passive diffusion of macromolecules across the blood-brain barrier in the absence of specific transporter (p.719, first column, last paragraph). Roopenian et al teach that vascular endothelium, including those in the brain, are the main sites that express FcRn (p.717, first colulmn, third paragraph). Roopenian et al teach that rather than transporting IgG into the CNS, **FcRn mediates reverse transport of IgG into the circulation from the brain**, as shown for IgG injected into the brain parenchyma (p.719, second column, first paragraph). Roopenian et al teach that in constrast to conventional Fc receptors for IgG, FcRn binds to the Fc region of IgG mainly at acidic pH 6-6.5, and not at pH 7.4 (p.720, second column). Thus in view of the teaching of Roopenian et al, one cannot predict that sufficient antibodies to SEQ ID No: 2, especially their FcRn variants that have increased binding to FcRn, as claimed in claims 56-59, 76-79, could reach gliomas, due to the problem with blood brain barrier, and active transporting of IgG from the brain into circulation, via FcRn receptor expressed in the brain vascular endothelium.

Further, it is well known in the art that cancer immunotherapy is highly unpredictable. White et al, 2001 (Ann Rev Med, 52: 125-145), teach that for a successful immunotherapy, besides the specificity of the antigen, other following properties of the antigen should also be considered: The antigen should be present on all or near all of the malignant cells to allow

effective targeting and to prevent a subpopulation of antigen-negative cells from proliferating. Further, antibodies have been developed against a broad spectrum of antigens, and whether the antigens shed, modulate or internalize influence the effectiveness of the administered antibody (p.126, second paragraph). Moreover, antigen internalization or downregulation can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p.126, paragraph before last). Furthermore, cancer tolerance is a well known phenomenon. Boon, 1992 (Adv Can Res, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, Boon teaches that even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells, such as loss of tumor antigen (p.198, first paragraph). Kirkin et al, 1998, APMIS, 106 : 665-679, teach that although several peptides of melanoma associated antigens have been identified as recognized by CTL in vitro, and in particular peptides from MAGE-A1 and MAGE-A3 have been tested for their ability to induce anti-melanoma immune response in vivo, so far only one of the peptides, peptide EVDPIGHLY of MAGE-A3, has limited anti-tumor activity, indicating their low immunogenicity (p.666, second column, second paragraph, last 6 lines). Smith RT, 1994 (Clin Immunol, 41(4): 841-849), teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches

that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limits the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specfic antigen in the necessary MHC context (p.484). Bodey et al, 2000, Anticancer Res, 20: 2665-2676, confirm the teaching of Boon and Smith, by explaining the reasons for failure of vaccine in human. Bodey et al teach that although general immune activation against the target antigens has been documented in most cases, reduction of tumor load has not been frequently observed in human patients (abstract, second column, p.2673). Bodey et al teach that the failure of cancer vaccine is due to natural selection of highly aggressive clones in the treated patient, said clones no longer express the cancer specific antigen (abstract, second column, p.2673). Bodey et al teach that these clones of tumor cells survive the immune system, through secretion of immunoinhibitory cytokines, downregulation of MHC, loss of costimulatory molecules, and induction of T cell anergy (p.2673, second column, last paragraph). Similarly, Lee et al, 1999, J Immunol, 163: 6292-6300, teach that although a quantifiable T-cell specific immune response is detected in melanoma patients, such a response does not associate with regression of metastatic melanoma (abstract, and Discussion on pages 6297-6299). Furthermore, Kaiser (Science, 2006, 313, 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Similarly, Gura, 1997, (Science, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Ezzell, 1995 (J. NIH Res, 7:46-49) reviews the current thinking in cancer

vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6).Thus, in view of the above teaching in the art, one cannot predict that the claimed method would successfully treat cancer, using an antibody to SEQ ID NO: 2.

2. Claims 43-81 are rejected under 112, first paragraph, for lack of enablement for **a method for treating glioma, using an antibody to a polypeptide having at least 80% identity to SEQ ID NO:2.**

Even if the claimed antibody to SEQ ID NO:2, including its Fc variants that have increased binding to FcRn, could be used successfully for treating gliomas, one cannot predict that an antibody to a polypeptide having at least 80% indentity with SEQ ID NO:2 could be used successfully for treating gliomas. One cannot predict that a polypeptide having at least 80% indentity with SEQ ID NO:2 would have the same property and characteristics of SEQ ID NO:2 and is overexpressed in gliomas, such that it could be used as a target for the antibody. It is well known in the art that variants of a sequence do not necessarily express at the same level as the corresponding wild type. For example, Schmid S et al, 2001 (J comparative Neurology, 430(2): 160-71), teach that the variants flip/flop of the gene GluR are expressed at higher levels in neurons in the auditory braistem, as compared to the wild type GluR-A and GluR-B, and that

neurons in the central nucleus of the inferior collicullus express high levels of GluR-B flip but only low levels of the other receptor subunits. Conner et al, 1996 (Mol Brain Res, 42: 1-17), teach that full length trkB is found the hippocampus in patients with Alzheimer's disease, but not in hippocampi of either normal age-matched individual or patients with Huntington's disease, and that truncated trkB is found in senile plaques in hippocampus and temporal lobe in both patients with Alzheimer's disease and Huntington's disease, but not in normal brains of aged-matched individuals (page 8, item 3.1.2). Thus in view of the teaching in the art one cannot predict that the at least 80% variants of SEQ ID NO: 2 would overexpress in gliomas as compared to normal control brain tissue, and therefore, one cannot predict that the claimed method would be successful in treating gliomas.

3. Claims 56-59, 76-79 are also rejected under 112, first paragraph, for lack of enablement for making **an antibody that has increased binding to FcRn**, using any amino acids recited in claims 56 or 76.

Even if the claimed antibody to SEQ ID NO:2, including its Fc variants that have increased binding to FcRn, could be used successfully for treating gliomas, one cannot predict that modification of any one or more amino acids in the Fc region of the antibody, as recited in claims 56, or 76, would result in an antibody to SEQ ID NO:2 with increased binding to FcRn for use in the claimed method, as contemplated in the specification. Shields et al, 2001, JBC, 276(9): 6591-6604, IDS of 07/15/05, teach that changes to Alanine of certain amino acids, such as Ile 253, Ser254, His435, and Tyr 436, or Arg 255, Lys 288, Ser 415, and His 433, abrogate or

reduce binding to FcRn (p.6597, second column, first paragraph). Amino acids Ile 253, Ser254, His435, and Tyr 436, Arg 255, Lys 288, Ser 415, and His 433 are recited in claims 56, 76.

MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the above unpredictability, and in view of the complex nature of the invention, a lack of sufficient disclosure in the specification, and little is known in the art concerning the claimed invention, there would be an undue quantity of experimentation required for one of skill in the art to practice the claimed invention, that is commensurate in scope of the claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
April 23, 2008

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643